

Ganciclovir

Brand Name: Cytovene, Cytovene-IV (sodium salt),
Microbial Infection and Other Drugs

Drug Class:

Drug Description

Ganciclovir is a synthetic purine nucleoside analogue of guanine. It is structurally and pharmacologically similar to acyclovir and is active against herpesviruses. [1] Compared to acyclovir, ganciclovir differs structurally such that it has substantially increased antiviral activity against cytomegalovirus (CMV) and less selectivity for viral DNA. [2]

HIV/AIDS-Related Uses

Ganciclovir was approved by the FDA on June 23, 1989. Parenteral ganciclovir is approved by the FDA for induction and maintenance treatment of CMV retinitis in patients with AIDS. Oral ganciclovir is approved for maintenance treatment of CMV retinitis in patients whose active retinitis was resolved by IV induction therapy. Oral ganciclovir is also approved for the prophylaxis of CMV disease in patients with advanced HIV infection who are at risk for developing CMV disease.[3]

The ganciclovir intravitreal implant was approved by the FDA on March 5, 1996, for the intraocular treatment of CMV retinitis in patients with AIDS.[4]

Non-HIV/AIDS-Related Uses

Parenteral ganciclovir is approved for treatment of CMV retinitis in immunocompromised patients. Oral ganciclovir is approved for maintenance treatment of CMV retinitis in immunocompromised patients who have stable retinitis after IV induction therapy and for disease prevention in solid organ transplant patients who are at risk for CMV retinitis.[5]

Pharmacology

Ganciclovir is a prodrug that is transformed into ganciclovir triphosphate by cellular kinases. The active phosphorylated form of ganciclovir inhibits replication of CMV and other human herpesviruses by interfering with DNA synthesis through competition with deoxyguanosine for incorporation

into viral DNA and by terminating DNA synthesis at the point of incorporation.[6] [7] Ganciclovir inhibits viral DNA polymerases more effectively than it does cellular polymerase. Chain elongation resumes when ganciclovir is removed. In CMV-infected cells, ganciclovir is thought to be phosphorylated much more rapidly than in uninfected cells; however, uninfected cells can also produce low levels of ganciclovir triphosphate.[8] Concentrations of ganciclovir triphosphate may be as much as 100-fold greater in CMV-infected than in uninfected cells and may persist for days in the CMV-infected cell.[9]

Ganciclovir is poorly absorbed from the gastrointestinal tract. The absolute bioavailability of oral ganciclovir under fasting conditions is about 5%, and about 6% to 9% when administered with food.[10] [11] In HIV infected individuals receiving 1 g of oral ganciclovir every 8 hours with food, the steady-state area under the concentration-time curve (AUC) increased by about 22%, peak serum concentrations (C_{max}) increased from 0.85 to 0.96 mcg/ml, and the time to peak concentration (T_{max}) increased from 1.8 to 3 hours as compared to fasting administration.[12]

Ganciclovir is widely distributed to all tissues and crosses the placenta; however, there is no marked accumulation in any one type of tissue.[13] Although the distribution of ganciclovir into human tissue and fluid is not fully understood, autopsy findings show that IV-administered ganciclovir concentrates in the kidneys, with lower concentrations in the lung, liver, brain, and testes. One study in individuals with normal renal function showed that steady-state distribution of the drug averaged 32.8 to 44.5 L/1.73 m² following IV administration. In individuals with renal impairment, distribution appears to be reduced. Ganciclovir crosses the blood-brain barrier; cerebrospinal fluid concentration of ganciclovir following IV administration averaged 41%.[14] The volume of distribution in adults and neonates is approximately 0.74 L/kg.[15]

Limited data show that ganciclovir has good intraocular distribution. Following IV administration, one adult had subretinal

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Pharmacology (cont.)

concentrations of ganciclovir of 0.87 and 2 times concurrent plasma concentrations at 5.5 and 8 hours, respectively. Concentrations of ganciclovir in the aqueous humor and the vitreous humor of another adult were 0.4 and 0.6 higher, respectively, than concurrent plasma concentrations at 2.5 hours following IV administration.[16]

Ganciclovir is in FDA Pregnancy Category C. There are no adequate or controlled studies in pregnant women; however, ganciclovir has been shown to be teratogenic in rabbits and embryotoxic in rabbits and mice. Based on this evidence, ganciclovir may be teratogenic and embryotoxic in humans when given at usual therapeutic dosages. It is not known whether ganciclovir is distributed into milk in humans; however, it is distributed into milk in laboratory animals and causes significant adverse effects in their offspring.[17] [18]

Ganciclovir is 1% to 2% bound to plasma proteins at drug concentrations of 0.5 to 51 mcg/ml. Other than intracellular phosphorylation, ganciclovir is not metabolized appreciably in humans. Serum half-life in individuals with normal renal function is 2.5 to 3.6 hours following IV administration and 3.1 to 5.5 hours following oral administration. In individuals with renal impairment, serum half-life is 9 to 30 hours following IV administration and 15.7 to 18.2 hours following oral administration. Approximately 90% to 99% of the drug is excreted unchanged in urine. Renal excretion of ganciclovir occurs mainly via glomerular filtration, although limited tubular secretion may also occur. Doses and frequency of administration of the drug should be modified according to creatinine clearance. Hemodialysis reduces plasma concentrations of ganciclovir by about 50%.[19]

Resistance to ganciclovir is defined as CMV with an in vitro median inhibitory concentration (IC₅₀) greater than 3.0 mcg/ml (12.0 microM). Resistance has been observed in patients receiving prolonged IV treatment for CMV retinitis. CMV resistance to ganciclovir has also been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. The principal mechanism of resistance to ganciclovir in CMV is the decreased ability to form the active triphosphate

moiety; resistant viruses have been described that contain mutations in the UL97 protein of CMV, which controls phosphorylation of ganciclovir. Mutations in the viral DNA polymerase have also been reported to confer viral resistance to ganciclovir.[20]

The ganciclovir intravitreal implant is designed to release ganciclovir over a period of 5 to 8 months. In one clinical trial, the median time to progression of CMV retinitis after insertion of the implant was 210 days. With the comparison treatment (recommended induction and maintenance doses of intravenous ganciclovir), the median time to progression of CMV retinitis was 120 days.[21]

Adverse Events/Toxicity

The most frequent and clinically significant adverse effects of oral and IV ganciclovir are granulocytopenia and thrombocytopenia, with incidences of approximately 40% and 20%, respectively. Both conditions are usually reversible. Other side effects reported with oral and IV ganciclovir use include anemia, central nervous system effects, hypersensitivity, phlebitis (for the IV form), and gastrointestinal disturbances.[22]

Retinal detachment can develop as a result of ganciclovir-induced resolution of retinitis and has been reported in up to 30% of ganciclovir-treated patients with CMV retinitis. This complication appears to occur more frequently in AIDS patients than in other immunosuppressed patients and may be related to the inability of AIDS patients to form firm scar tissue, secondary to impaired inflammatory responses, as the retina heals.[23] Other side effects observed with use of the ganciclovir intravitreal implant include bacterial endophthalmitis, mild conjunctival scarring, foreign body sensation, retinal detachment, scleral induration, and subconjunctival hemorrhage.[24] Blurred or decreased vision has been known to occur following insertion of the intravitreal implant and may last 2 to 4 weeks after insertion of the implant. For the first 2 months after surgery, patients may see flashes or sparks of light, floating spots before the eyes, or a veil or curtain appearing across part of their vision. They may also have eye pain or tearing; red or bloodshot eyes; or sensitivity to light. Patients are encouraged to seek medical

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Adverse Events/Toxicity (cont.)

attention if they experience any side effects.[25]

In animal studies, ganciclovir was carcinogenic and teratogenic and caused aspermatogenesis. Usual doses of ganciclovir are likely to cause temporary or permanent inhibition of spermatogenesis in men and may suppress fertility in women. Because of ganciclovir's high toxicity and mutagenic and teratogenic potential, use in pregnant women should be avoided. In addition, women of childbearing age should use effective contraception while taking ganciclovir. Men should use barrier contraception during treatment and for at least 90 days following treatment.[26]

Because solutions of ganciclovir are alkaline (pH 11), direct contact of capsule powder or parenteral solution with skin or with mucous membranes can cause irritation or burning.[27]

Drug and Food Interactions

Ganciclovir capsules should be taken with food for maximum absorption.[28]

Blood dyscrasia-causing medications, bone marrow depressants, and radiation therapy should not be taken concurrently with ganciclovir. Concurrent use of these medications may increase the bone marrow depressant effects of these medications and radiation therapy.[29]

Nephrotoxic medications should not be used with ganciclovir. Concurrent use of these medications with ganciclovir may increase serum creatinine. Taking ganciclovir with certain nephrotoxic medications, such as cyclosporine or amphotericin B, may increase the chance of renal function impairment, which could subsequently decrease ganciclovir elimination and increase the risk of toxicity.[30]

Concurrent use of ganciclovir and zidovudine has been associated with severe hematologic toxicity in some patients, even when the zidovudine dose was reduced to 300 mg/day. If ganciclovir and zidovudine are administered together, the AUC of zidovudine increases by 14% to 19%. In vitro studies have found concurrent use of these two

drugs to be synergistically cytotoxic, so concurrent administration should be approached with caution.[31]

Ganciclovir has exhibited additive or synergistic antiviral activity with foscarnet against CMV and herpes simplex virus type 2 (HSV-2). Combined therapy may be effective in treatment of CMV infection that is resistant to either drug alone.[32]

Contraindications

Risk-benefit should be considered in patients with absolute neutrophil counts (ANCs) less than 500 cells/mm³ or platelet counts of less than 25,000 cells/mm³. Because ganciclovir is excreted through the kidneys, the ganciclovir dose may need to be reduced or the dosing interval increased in patients with renal function impairment. Ganciclovir is also contraindicated in patients with hypersensitivity to ganciclovir or acyclovir.[33]

Patients with contraindications for intraocular surgery, such as external infection or severe thrombocytopenia, should not receive ganciclovir intravitreal implants.[34]

Because oral ganciclovir is associated with a risk of more rapid rate of CMV retinitis progression, it should be used as maintenance treatment only in those patients for whom this risk is balanced by the benefit of avoiding daily IV infusions.[35]

Clinical Trials

For information on clinical trials that involve Ganciclovir, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Ganciclovir AND HIV Infections.

Dosing Information

Mode of Delivery: Oral, intravenous[36] , or intravitreal.[37]

Dosage Form: Ganciclovir capsules containing 250 mg and 500 mg.[38]

Ganciclovir sodium for injection in 10 ml sterile vials, each containing the equivalent of 500 mg of ganciclovir.[39]

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Dosing Information (cont.)

Intravitreal implant containing 4.5 mg ganciclovir, with magnesium stearate 0.25% and polyvinyl alcohol and ethylene vinyl acetate polymers.[40]

Storage: Ganciclovir capsules should be stored between 5 C and 25 C (41 F and 77 F). Ganciclovir sodium vials for injection should be stored below 40 C (104 F) and protected from freezing.[41] Ganciclovir intravitreal implants should be stored between 15 C and 30 C (59 F and 86 F) and protected from freezing and from excessive heat and light.[42]

Chemistry

CAS Name: Ganciclovir: 6H-Purin-6-one,2-amino-1,9-dihydro-9-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-[43]

Ganciclovir sodium: 6H-Purin-6-one,1,9-dihydro-2-amino-9-((2-hydroxy-1-(hydroxymethyl)ethoxy)methyl)-, monosodium salt[44]

CAS Number: Ganciclovir: 82410-32-0[45]

Ganciclovir sodium: 107910-75-8[46]

Molecular formula: Ganciclovir: C₉-H₁₃-N₅-O₄; Ganciclovir sodium: C₉-H₁₂-N₅-NaO₄[47]

Ganciclovir: C42.35%, H5.13%, N27.44%, O25.07%; Ganciclovir sodium: C38.99%, H4.36%, N25.26%, O23.09%, Na8.30%[48]

Molecular weight: Ganciclovir: 255.23; Ganciclovir sodium: 277.21[49]

Melting point: 250 C[50]

Physical Description: White to off-white crystalline lyophilized powder.[51]

Stability: Ganciclovir, when reconstituted with sterile water for injection, further diluted with 0.9% sodium chloride for injection, and stored refrigerated at 5 C (41 F) in polyvinyl chloride (PVC) bags, remains physically and chemically stable for 14 days. However, because ganciclovir for infusion is reconstituted with nonbacteriostatic

sterile water, it is recommended that the infusion solution be used within 24 hours of dilution to reduce the risk of bacterial contamination. The infusion should be refrigerated; freezing is not recommended.[52]

Solubility: Ganciclovir has a solubility of 4.3 mg/ml in water at 25 C and neutral pH. Ganciclovir and ganciclovir sodium are freely soluble in water at high pH and less soluble at more neutral pH, although crystallization may occur in concentrated solutions of the drug exceeding 10 mg/ml.[53]

Other Names

BW-759[54]

RS-21592[55]

Biof 62[56]

Gancyclovir[57]

BW 759[58]

Further Reading

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Manufacturer Information

Ganciclovir
Roche Laboratories
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Cytovene-IV (sodium salt)
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Vitrasert
Bausch & Lomb Surgical Inc
555 West Arrow Highway
Claremont, CA 91711
(800) 531-2020

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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